Remarks

Information Disclosure Statement (IDS)

The Examiner indicated that the U.S. Patents cited on the IDS in Paper No. 6 were considered and initialed on the 1449 by the Examiner but that if Applicants want the U.S. Patents to be printed should the application be allowed, a 1449 listing the class/subclass for each U.S. Patent must be submitted. Accordingly, Applicants submit herewith a replacement Form 1449 form so listing only the U.S. Patents previously cited, considered, and initialed by the Examiner on the 1449 in Paper No. 6. Applicants respectfully request that the U.S. Patents cited in the IDS be printed should the application be allowed.

Applicants note that the Examiner indicated (page 11) that reference B5 listed on the 1449 in Paper No. 6 was accidentally crossed out by the Examiner and has been considered by the Examiner.

Drawings

The Examiner indicated that the draftsman objected to the drawings. A complete set of formal drawings is filed herewith. Applicants request entry of the formal drawings.

Specification

Applicants request entry of the enclosed substitute specification, incorporating all previous amendments, as well as new amendments to the written description described below and intended to address the objections raised by the Examiner. No new matter has been introduced.

The Examiner indicated that the Specification as filed was objected to because ODN GR1 on original page 30, last line, was not labeled as SEQ ID NO:17; the abstract did not commence on a separate sheet apart from any other text; and section headings were missing.

In response, section headings have been added. The first paragraph on original page 1 has been moved down to a new section entitled Summary of the Invention beginning on new page 7; the same paragraph is also presented as the text of the abstract, which appears on a separate sheet (new page 60). The description of the figures on original pages 22-24 has been moved up to a new section entitled Brief Description of the Figures, beginning on new page 8.

The G-motif ODN GR1 has been labeled as SEQ ID NO:17 where it appears in Example 11 on new page 32.

Applicants believe the substitute specification filed herewith addresses the objections raised by the Examiner. Accordingly, Applicants request the Examiner to withdraw his objections to the specification.

Claim Rejections – 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 104-116 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement for a method of treating a tumor in a subject comprising administering to a subject having a tumor an oligonucleotide comprising the sequence N_1-N_2-G-N_3-G, wherein N_2 and N_3 are not G. Applicants acknowledge that the Examiner indicated, however, that a method of treating a tumor in a subject comprising administering to a subject having a tumor an oligonucleotide comprising the sequence N_1-N_2-G-N_3-G, wherein N_2 and N_3 are G, wherein the oligonucleotide does not comprise a CG dinucleotide, is enabled. The Examiner cites Lipford et al. (2000) *Immunology* 101:46-52 for the proposition that at least four, but not less than four consecutive G bases are required for T-cell stimulation. The Examiner further asserts that the specification does not provide sufficient guidance or factual evidence for one skilled to use an oligonucleotide comprising the sequence selected from the group consisting of GAGGG, GGGAG, GTGGG, or GGGTG to treat a tumor in a subject. Applicants respectfully disagree, for reasons below.

The clear intent of the language of claim 104 is to point out that, contrary to the later teaching of Lipford et al., a poly-G sequence in which any four of five consecutive nucleotides N_1-N_2-G-N_3-G are G is useful in a method of treating a subject having a tumor, as claimed. In other words, a poly-G sequence N_1-N_2-G-N_3-G in which at least two of N_1, N_2, and N_3 are G is useful in a method of treating a subject having a tumor, as claimed. Such a sequence can include a sequence G-N_2-G-G-G or G-G-G-N_3-G, in which there are three consecutive G nucleotides. Alternatively, such a sequence can include N_1-G-G-G-G, in which there are four consecutive G nucleotides, or G-G-G-G-G, in which there are five consecutive G nucleotides.

Without meaning to concede the rejection of the Examiner, claim 104 has been amended to recite the limitation that at least two of N_1, N_2, and N_3 are G. With such an amendment there should remain no doubt in the mind of the Examiner that the claim does not read on a method

involving use of an oligonucleotide comprising the sequence N_1-N_2-G-N_3-G, wherein N_2 and N_3 are not G, because either or both of N_2 and N_3 must be G according to claim 104 as amended.

Furthermore, Applicants respectfully wish to point out to the Examiner that the priority date for the instant application is September 3, 1998, fully two years before the publication date of the cited reference of Lipford et al. (2000) *Immunology* 101:46-52. Therefore, contrary to the Examiner's assertion, the state of the art at the time the application was originally filed did not include the reference of Lipford et al.

In addition, the specification clearly teaches, for example in Example 9, that an oligonucleotide including the G-motif GTGGG (PZ35, SEQ ID NO:6) is costimulatory for T cells. The specification also teaches, for example in Example 9, that an oligonucleotide including the G-motif GGGTG (PZ33, SEQ ID NO:5) is costimulatory for T cells, albeit to a lesser degree than PZ35. These are to be compared to the results provided, again in Example 9, for G-motifs GGGGG (PZ3, SEQ ID NO:3) and TGGGG (PZ32 and PZ36, SEQ ID NOs:4 and 7, respectively), which are disclosed as highly costimulatory. One of skill in the art would recognize that all of these G-motifs would be useful in a method of treating a tumor in a subject, as claimed, although some may be more potent than others.

The Examiner also objected to the alleged scope of the term "subject". Specifically, the Examiner asserts that the art of record teaches that vertebrate subjects respond to poly-G nucleic acids but the art of record and the specification are absent about non-vertebrate subjects responding to a poly-G nucleic acid. In response, Applicants note first that those of skill in the art would understand that the claims are intended to encompass only vertebrate subjects. For example, the first sentence of the application as amended states that cells of the immune system are exported from the bone marrow and undergo a series of differentiation events which confer upon them the capacity to recognize and control foreign pathogens and cancer cells by discriminating between self versus non-self. It is clear to the reader that only vertebrates have bone marrow. Second, it is to be noted that the examples in the specification are directed to vertebrate subjects. Thus the scope of the term "subject", while not explicitly set forth as such, is understood to encompass only vertebrate subjects.

The foregoing notwithstanding, and in order to advance prosecution, Applicants have amended claim 104 to specify that the subject is a vertebrate.

Applicants have amended claim 104 to recite the limitation that at least two of N_1, N_2, and N_3 of the G-motif N_1-N_2-G-N_3-G are G in order to overcome the Examiner's rejection of claims 104-116 under 35 U.S.C. § 112, first paragraph. Applicants believe that the remaining grounds for the rejection for alleged lack of enablement have been addressed and overcome. Accordingly, Applicants respectfully request the Examiner to withdraw his rejection of claims 104-116 under 35 U.S.C. § 112, first paragraph.

Claim Rejections -- 35 U.S.C. § 102(e)

The Examiner rejected claims 104-106 and 109-115 under pre-AIPA 35 U.S.C. § 102(e) as being anticipated by Zupi (U.S. Pat. No. 6,080,727). Zupi specifically teaches the use of sequence-specific antisense oligonucleotides complementary to human c-myc mRNA for the inhibition of human melanoma tumor growth. Some of the oligonucleotides disclosed in Zupi (SEQ ID NOs:10 and 13-17) do contain G-quartets, i.e., four contiguous guanosine residues, and do not contain CG dinucleotides. Zupi emphasizes that the G quartet structure alone is not sufficient to inhibit melanoma tumor growth because control oligonucleotides having scrambled sequence (relative to c-myc mRNA) and a G quartet were not effective, according to Zupi, to inhibit human melanoma tumor growth. See, for example, Zupi Figure 1A-1C; Figure 3B and 3C; column 8, lines 58-60; column 12, lines 60-62; column 19, lines 46-47; and column 22, lines 36-38.

The disclosure of Zupi represents at most an accidental anticipation of the claimed method. In contrast to Zupi, the instantly claimed invention does not require a sequence-specific antisense oligonucleotide complementary to human mRNA to practice the claimed method. The claimed method calls for administering to a subject having a tumor an oligonucleotide comprising the suitable poly-G motif and excluding a CG dinucleotide, in an effective amount to treat the tumor. Zupi calls for sequence-specific antisense oligonucleotides complementary to human c-myc mRNA. There is no a priori reason to expect that one skilled in the art would necessarily choose a sequence-specific antisense oligonucleotide complementary to human c-myc mRNA that meets all the limitations of the claimed method, namely, the sequence-specific antisense oligonucleotides complementary to human c-myc mRNA would have to be free of CG dinucleotide and include a sequence N_1-N_2-G-N_3-G in which at least any two of N_1, N_2, and N_3 are G.

Zupi also generally does not anticipate the claimed methods because antisense methods require substantially larger doses of oligonucleotide than do the claimed methods. For example, Zupi discloses 100 μg/ml for in vitro assays (Examples 4 and 5); 250-1000 μg/day i.v. for eight consecutive days in mice (22-24 g body weight; Example 8); and 100-1,000,000 μg/day in humans (column 12, lines 45-46). In contrast, dosing in the instant specification is disclosed as 0.001-1000 μg for a human (page 12, line 24 in original). Examples 6-8 disclose administration of 10 nmol of PZ2 (predicted molecular weight 6424.2 g/mol) to individual mice, i.e., 64 μg/mouse. Thus, the doses useful according to the claimed methods are many times smaller than the doses called for in Zupi.

In view of the foregoing, Applicants believe that Zupi does not anticipate, or at most only accidentally anticipates, claims 104-106 and 109-115. Accordingly, Applicants respectfully request the Examiner to withdraw the rejection of claims 104-106 and 109-115 under pre-AIPA 35 U.S.C. § 102(e).

Claim Rejections -- 35 U.S.C. § 102(b)

The Examiner rejected claims 104, 105, 107-110, and 114 under 35 U.S.C. § 102(b) as being anticipated by Iversen et al. (U.S. Pat. No. 5,643,890). Iversen specifically teaches contacting cells, characterized by uncontrolled proliferation or by telomerase expression, with an oligonucleotide comprising a sequence of, or substantially similar to, a single human telomeric repeat motif. In one embodiment the telomere motif is TGAGGG (claims 8 and 25). In one embodiment the telomere motif TGAGGG is present in a 9-mer TGTGAGGGG (Example 2, column 11). The Examiner did not reject instant claims 111-113, drawn to methods using oligonucleotides comprising the requisite poly-G motif, in which the oligonucleotide is 10-50, 13-30, or 17-21 nucleotides long. Accordingly, Applicants have amended claim 104 to incorporate the limitation of claim 111, such that the oligonucleotide is 10-50 nucleotides long. Because amended claims 104, 105, 107-110, and 114 clearly are not anticipated by Iversen et al., Applicants respectfully request that the rejection of claims 104, 105, 107-110, and 114 under 35 U.S.C. § 102(b) be withdrawn.

Claim Rejections -- 35 U.S.C. § 103(a)

The Examiner rejected claims 104 and 116 under 35 U.S.C. § 103(a) as being unpatentable over either Iversen et al. (U.S. Pat. No. 5,643,890) or Zupi (U.S. Pat. No. 6,080,727) taken with Kuby (Immunology, 2nd edition, W.H. Freeman Company, 1994). More specifically, the Examiner asserts that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine a tumor-specific antigen with an oligonucleotide according to the teaching of Zupi or Iversen to treat a tumor in a subject. In response, Applicants first note that the rejection would not appear to apply to claim 104, which makes no reference to tumor-specific antigens. Furthermore, in light of the arguments and amendments set forth above in response to the claim rejections under 35 U.S.C. § 102(e) and 35 U.S.C. § 102(b), relating to the Zupi and Iversen references, respectively, Applicants respectfully submit that the Examiner has failed to make a prima facie case for rejection of claim 116 under 35 U.S.C. § 103(a). Applicants therefore respectfully request withdrawal of the rejection of claims 104 and 116 under 35 U.S.C. § 103(a).

Summary

A substitute specification is provided. Arguments and amendments to the specification and claims are made in response to the Office Action mailed March 24, 2003. It is believed that the claims are in condition for allowance. A prompt and favorable action is earnestly solicited.

Respectfully submitted,

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Docket No: C01041.70010.US
Date: September 22, 2003
X: September 24, 2003